27,962

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No. 4278689
Issued July 14, 1981

#19

Inventors: Keith C. Murdock
Frederick E. Durr

Assignee: AMERICAN CYANAMID COMPANY, One Cyanamid Plaza, Wayne, New Jersey 07470

Title: 1,4-Bis(Substituted-Amino)-5,8-Dihydroxyanthraquinones and Leuco Bases Thereof

Commissioner of Patents
and Trademarks
Box Patent Term Extension
Washington, D.C. 20231

SIR:

SUPPLEMENT TO
APPLICATION FOR EXTENSION
OF PATENT TERM

Supplemental to the APPLICATION FOR EXTENSION OF PATENT TERM of U.S. Patent No. 4278689, there is submitted herewith a copy of the F.D.A. approval letter for the approved product and a package insert. These submissions further demonstrate the correlation between the approved product and the claims of U.S. Patent No. 4278689.

Respectfully submitted,

Edward A. Conroy, Jr.

Edward A. Conroy, Jr.
Registration No. 19,087

American Cyanamid Company
Patent Law Department
1937 West Main Street
P.O. Box 60
Stamford, CT 06904

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D. C. 20231, on FEBRUARY 19, 1988
(Date of Deposit)

EDWARD A. CONROY, JR.
Name of Applicant, Assignee, or Registered Representative

Edward A. Conroy, Jr.
Signature

19-II-88

EAC/jhr
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ST-82 11/79

OVERDOSAGE

There is no known specific antidote for NOVANTRONE. Accidental overdoses have been reported. Four patients receiving 140 - 180 mg/M² as a single bolus injection died as a result of severe leukopenia with infection. Hematologic support and antimicrobial therapy may be required during prolonged periods of medullary hypoplasia.

Although patients with severe renal failure have not been studied, NOVANTRONE is extensively tissue bound and it is unlikely that the therapeutic effect or toxicity would be mitigated by peritoneal or hemodialysis.

DOSAGE AND ADMINISTRATION (See WARNINGS)

NOVANTRONE SOLUTION MUST BE DILUTED PRIOR TO USE.

Combination Initial Therapy for ANLL in Adults: For induction, the recommended dosage is 12 mg/M² of NOVANTRONE daily on Days 1-3 given as an intravenous infusion, and 100 mg/M² of cytosine arabinoside for seven days given as a continuous 24 hour infusion on Days 1-7.

Most complete remissions will occur following the initial course of induction therapy. In the event of an incomplete antileukemic response, a second induction course may be given. NOVANTRONE should be given for two days and cytosine arabinoside for five days using the same daily dosage levels.

If severe or life-threatening nonhematologic toxicity is observed during the first induction course, the second induction course should be withheld until toxicity clears.

Consolidation therapy which was used in two large randomized multicenter trials consisted of NOVANTRONE 12 mg/M² given by intravenous infusion daily for days 1 and 2, and cytosine arabinoside, 100 mg/M² for 5 days given as a continuous 24 hour infusion on days 1-5. The first course was given approximately 6 weeks after the final induction course, the second was generally administered 4 weeks after the first. Severe myelosuppression occurred. (See CLINICAL PHARMACOLOGY Section).

NOVANTRONE solution should be diluted to at least 50 mL with either 0.9% Sodium Chloride Injection (USP) or 5% Dextrose Injection (USP). This solution should be introduced slowly into the tubing as a freely running intravenous infusion of 0.9% Sodium Chloride Injection (USP) or 5% Dextrose Injection (USP) over a period of not less than 3 minutes. Unused infusion solutions should be discarded in an appropriate fashion. If extravasation occurs, the administration should be stopped immediately and restarted in another vein. The nonvesicant properties of NOVANTRONE minimize the possibility of severe local reactions following extravasation. However, care should be taken to avoid extravasation at the infusion site and to avoid contact of NOVANTRONE with the skin, mucous membranes or eyes.

Skin accidentally exposed to NOVANTRONE should be rinsed copiously with warm water and if the eyes are involved, standard irrigation techniques should be used immediately. The use of goggles, gloves, and protective gowns is recommended during preparation and administration of the drug. Spills on equipment and environmental surfaces may be cleaned using an aqueous solution of calcium hypochlorite (5.5 parts calcium hypochlorite in 13 parts by weight of water for each 1 part of NOVANTRONE). Absorb the solution with gauze or towels and dispose of these in a safe manner. Appropriate safety equipment such as goggles and gloves should be worn while working with calcium hypochlorite.

NOVANTRONE should not be mixed in the same infusion as heparin since a precipitate may form. Because specific compatibility data are not available, it is recommended that NOVANTRONE not be mixed in the same infusion with other drugs.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-6] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA, March 15, 1985.
3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc. D., Director of Pharmacy Services, Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02902.
4. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. Med J Australia 1:426-428 1983.
5. Jones R.B., et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. Ca - A Cancer Journal for Clinicians Sept/Oct. 258-263 1983.
6. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic drugs in hospitals. Am J Hosp Pharm 42:131-137 1985.

NOVANTRONE may be further diluted into Dextrose 5% in Water, Normal Saline or Dextrose 5% with Normal Saline and used immediately. DO NOT FREEZE.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

NOVANTRONE® mitoxantrone hydrochloride concentrate for Injection is a sterile aqueous solution at a concentration equivalent to 2 mg mitoxantrone free base per mL and is supplied in vials for single dose use as follows:

NDC 0005-9393-34 - 10 mL/vial (20 mg)
NDC 0005-9393-72 - 12.5 mL/vial (25 mg)
NDC 0005-9393-36 - 15 mL/vial (30 mg)

NOVANTRONE is stable for two years from time of manufacture. NOVANTRONE should be stored at Controlled Room Temperature 15-30°C (59-86°F). DO NOT FREEZE.

Manufactured by
LEDERLE LABORATORIES DIVISION
Cyanamid of Great Britain Ltd.
Gosport, Hampshire, England
Distributed by
LEDERLE LABORATORIES DIVISION
American Cyanamid Company,
Pearl River, NY 10965

REV. 12/87

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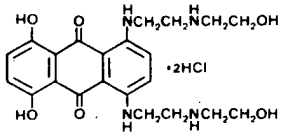
NOVANTRONE®

Mitoxantrone Hydrochloride Concentrate For Injection

DESCRIPTION

NOVANTRONE® mitoxantrone hydrochloride is a synthetic antineoplastic anthracenedione for intravenous use. Its molecular formula is $C_{22}H_{28}N_4O_6.2HCl$ and its molecular weight is 517.4. It is supplied as a concentrate which MUST BE DILUTED PRIOR TO INJECTION. The concentrate is a sterile, dark blue aqueous solution containing mitoxantrone hydrochloride equivalent to 2 mg/mL mitoxantrone free base, with sodium chloride (0.80% w/v), sodium acetate (0.005% w/v), and acetic acid (0.046% w/v) as inactive ingredients. The solution has a pH of 3.0 to 4.5 and contains 0.14 mEq of sodium per ml. The product does not contain preservatives. Its structural formula appears below.



1,4-Dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino-9, 10-anthracenedione dihydrochloride

CLINICAL PHARMACOLOGY

Although its mechanism of action is not fully elucidated, NOVANTRONE is a DNA-reactive agent. It has a cytocidal effect on both proliferating and nonproliferating cultured human cells, suggesting lack of cell cycle phase specificity. Pharmacokinetic studies have not been performed in humans receiving multiple daily doses. Pharmacokinetic studies in adult patients following a single intravenous administration of NOVANTRONE have demonstrated multi-exponential plasma clearance. Distribution to tissues is rapid and extensive. Distribution to the brain, spinal cord, eye, and spinal fluid in the monkey is low. The apparent steady state volume of distribution exceeds 1000L/M². Elimination of drug is slow with an apparent mean terminal plasma half-life of 5.8 days (range 2.3-13.0). The half-life in tissues may be longer. Multiple intravenous doses in dogs daily for five days resulted in significant accumulation in plasma and tissue. The extent of accumulation was four fold.

NOVANTRONE is 78% bound to plasma proteins in the observed concentration range of 26-455 ng/mL. This binding is independent of concentration and was not affected by the presence of diphenylhydantoin, doxorubicin, methotrexate, prednisone, prednisolone, heparin, or acetylsalicylic acid.

NOVANTRONE is excreted via the renal and hepatobiliary systems. Renal excretion is limited; only - 11% of the dose is recovered in the urine within .. days after drug administration. Of the material recovered in the urine, 65% is unchanged drug; the remaining 35% is comprised primarily of two inactive metabolites and their glucuronide conjugates. The metabolites are mono- and dicarboxylic acid derivatives. Hepatobiliary elimination of drug appears to be of greater significance with as much as 25% of the dose recovered in the feces within five days of intravenous dosing. No significant difference in the pharmacokinetics of NOVANTRONE was observed in 7 patients with moderately impaired liver function (serum bilirubin 1.3-3.4 mg/dL) as compared with 16 patients without hepatic dysfunction. Results of pharmacokinetic studies on 4 patients with severe hepatic dysfunction (bilirubin greater than 3.4 mg/dL) suggest that these patients have a lower total body clearance and a larger Area under Curve than other patients at a comparable NOVANTRONE dose.

In two large randomized multicenter trials, remission induction therapy for ANLL with NOVANTRONE 12 mg/M² daily for three days as a 10-minute intravenous infusion and cytosine arabinoside 100 mg/M² for seven days given as a continuous 24 hour infusion was compared with daunorubicin 45 mg/M² daily by intravenous infusion for three days plus the same dose and schedule of cytosine arabinoside used with NOVANTRONE. Patients who had an incomplete antileukemic response received a second induction course in which NOVANTRONE or daunorubicin was given for two days and cytosine arabinoside for five days using the same daily dosage schedule. Response rates and median survival information for both the U.S. and international multicenter trials are given in the following table:

Trial	% Complete Response(CR)		Median Time to CR (days)		Median Survival (days)	
	NOV	DAUN	NOV	DAUN	NOV	DAUN
U.S	63 (62/98)	53 (54/102)	35	42	312	237
Foreign	50 (56/112)	51 (62/123)	36	42	192	230

NOV = NOVANTRONE® + Cytosine arabinoside
DAUN = Daunorubicin + Cytosine arabinoside

In these studies, two consolidation courses were administered to complete responders on each arm. Consolidation therapy consisted of the same drug and daily dosage used for remission induction, but only 5 days of cytosine arabinoside and 2 days of NOVANTRONE or daunorubicin were given. The first consolidation course was administered 6 weeks after the start of the final induction course if the patient achieved a com-

plete remission. The second consolidation course was generally administered 4 weeks later. Full hematologic recovery was necessary for patients to receive consolidation therapy. For the U.S. trial, median granulocyte nadirs for patients receiving NOVANTRONE + cytosine arabinoside for consolidation courses 1 and 2 were 10/mm³ for both courses, and for those patients receiving daunorubicin + cytosine arabinoside were 170/mm³ and 260/mm³, respectively. Median platelet nadirs for patients who received NOVANTRONE + cytosine arabinoside for consolidation courses 1 and 2 were 17,000/mm³ and 14,000/mm³, respectively, and were 33,000/mm³ and 22,000/mm³ in courses 1 and 2 for those patients who received daunorubicin + cytosine arabinoside. The benefit of consolidation therapy in ANLL patients who achieve a complete remission remains controversial. However, in the only well controlled prospective, randomized multicenter trials with NOVANTRONE in ANLL, consolidation therapy was given all patients who achieved a complete remission. During consolidation in the U.S. study, two myelosuppression related deaths occurred on the NOVANTRONE arm and one on the daunorubicin arm. However, in the foreign study there were eight deaths on the NOVANTRONE arm during consolidation which were related to the myelosuppression and none on the daunorubicin arm where less myelosuppression occurred.

INDICATIONS AND USAGE

NOVANTRONE in combination with other approved drug(s) is indicated in the initial therapy of acute nonlymphocytic leukemia (ANLL) in adults. This category includes myelogenous, promyelocytic, monocytic, and erythroid acute leukemias.

CONTRAINDICATIONS

NOVANTRONE is contraindicated in patients who have demonstrated prior hypersensitivity to it.

WARNINGS

WHEN NOVANTRONE IS USED IN DOSES INDICATED FOR THE TREATMENT OF LEUKEMIA, SEVERE MYELOSUPPRESSION WILL OCCUR. THEREFORE, IT IS RECOMMENDED THAT NOVANTRONE BE ADMINISTERED ONLY BY PHYSICIANS EXPERIENCED IN THE CHEMOTHERAPY OF THIS DISEASE. LABORATORY AND SUPPORTIVE SERVICES MUST BE AVAILABLE FOR HEMATOLOGIC AND CHEMISTRY MONITORING AND ADJUNCTIVE THERAPIES, INCLUDING ANTIBIOTICS: BLOOD AND BLOOD PRODUCTS MUST BE AVAILABLE TO SUPPORT PATIENTS DURING THE EXPECTED PERIOD OF MEDULLARY HYPOPLASIA AND SEVERE MYELOSUPPRESSION. PARTICULAR CARE SHOULD BE GIVEN TO ASSURING FULL HEMATOLOGIC RECOVERY BEFORE UNDERTAKING CONSOLIDATION THERAPY (IF THIS TREATMENT IS USED) AND PATIENTS SHOULD BE MONITORED CLOSELY DURING THIS PHASE.

Patients with pre-existing myelosuppression as the result of prior drug therapy should not receive NOVANTRONE unless it is felt that the possible benefit from such treatment warrants the risk of further medullary suppression. Because of the possible danger of cardiac effects in patients previously treated with daunorubicin or doxorubicin, the benefit-to-risk ratio of NOVANTRONE therapy in such patients should be determined before starting therapy.

The safety of NOVANTRONE in patients with hepatic insufficiency is not established. (See CLINICAL PHARMACOLOGY).

Cardiac Effects

General - Functional cardiac changes including congestive heart failure and decreases in left ventricular ejection fraction (LVEF) occur with NOVANTRONE. Cardiac toxicity may be more common in patients with prior treatment with anthracyclines, prior mediastinal radiotherapy, or with pre-existing cardiovascular disease. Such patients should have regular cardiac monitoring of LVEF from the initiation of therapy. In investigational trials of intermittent single doses in other tumor types, patients who received up to the cumulative dose of 140 mg/M² had a cumulative 2.6% probability of clinical congestive heart failure. The overall cumulative probability rate of moderate or serious decreases in LVEF at this dose was 13% in comparative trials.

Leukemia - Acute CHF may occasionally occur in patients treated with NOVANTRONE for ANLL. In first-line comparative trials of NOVANTRONE + cytosine arabinoside vs daunorubicin + cytosine arabinoside in adult patients with previously untreated ANLL, therapy was associated with congestive heart failure in 6.5% of patients on each arm. A causal relationship between drug therapy and cardiac effects is difficult to establish in this setting since myocardial function is frequently depressed by the anemia, fever and infection, and hemorrhage which often accompany the underlying disease.

Pregnancy Category D - NOVANTRONE may cause fetal harm when administered to a pregnant woman. In treated rats, low fetal birth weight and retarded development of the fetal kidney were seen in greater frequency. In rabbits, an increased incidence of premature delivery was observed. NOVANTRONE was not teratogenic in rabbits. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Safety for use by routes other than intravenous administration has not been established.

PRECAUTIONS

General: Therapy with NOVANTRONE should be accompanied by close and frequent monitoring of hematologic and chemical laboratory parameters, as well as frequent patient observation.

Hyperuricemia may occur as a result of rapid lysis of tumor cells by NOVANTRONE. Serum uric acid levels should be monitored and hypouricemic therapy instituted prior to the initiation of antileukemic therapy.

Systemic infections should be treated concomitantly with or just prior to commencing therapy with NOVANTRONE.

Information for Patients: NOVANTRONE may impart a blue-green color to the urine for 24 hours after administration, and patients should be advised to expect this during therapy. Bluish discoloration of the sclera may also occur. Patients should be advised of the signs and symptoms of myelosuppression.

Laboratory Tests: Serial complete blood counts and liver function tests are necessary for appropriate dose adjustments. (See DOSAGE AND ADMINISTRATION section.)

Carcinogenesis, Mutagenesis: NOVANTRONE can result in chromosomal aberrations in animals and it is mutagenic in bacterial systems. NOVANTRONE caused DNA damage and sister chromatid exchanges *in vitro*.

Pregnancy Category D (See WARNINGS section.)

Nursing Mothers: It is not known whether NOVANTRONE is excreted in human milk. Because of the potential for serious adverse reactions in infants from NOVANTRONE, breast feeding should be discontinued before starting treatment.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

NOVANTRONE has been studied in approximately 600 patients with acute nonlymphocytic leukemia. The table below represents the adverse reaction experience in the large U.S. comparative study of mitoxantrone plus cytosine arabinoside *vs* daunorubicin plus cytosine arabinoside. Experience in the large foreign study was similar. A much wider experience in a variety of other tumor types revealed no additional important reactions other than cardiomyopathy (See WARNINGS). It should be appreciated that the listed adverse reaction categories include overlapping clinical symptoms related to the same condition e.g. dyspnea, cough and pneumonia. In addition, the listed adverse reactions cannot all necessarily be attributed to chemotherapy as it is often impossible to distinguish effects of the drug and effects of the underlying disease. It is clear, however, that the combination of NOVANTRONE plus cytosine arabinoside was responsible for nausea and vomiting, alopecia, mucositis/stomatitis, and myelosuppression.

The following table summarizes adverse reactions occurring in patients treated with NOVANTRONE + cytosine arabinoside in comparison with those who received daunorubicin + cytosine arabinoside for therapy of ANLL in a large multicenter randomized prospective U.S. trial. Adverse reactions are presented as major categories and selected examples of clinically significant subcategories.

	ALL INDUCTION [percentage of pts entering induction]		ALL CONSOLIDATION [percentage of pts entering consolidation]	
	NOV N=102	DAUN N=102	NOV N=55	DAUN N=49
Cardiovascular	26	28	11	24
CHF	5	6	0	0
Arrhythmias	3	3	4	4
Bleeding	37	41	20	6
GI	16	12	2	2
petechiae/ecchymoses	7	9	11	2
Gastrointestinal	88	85	58	51
Nausea/Vomiting	72	67	31	31
Diarrhea	47	47	18	8
Abdominal Pain	15	9	9	4
Mucositis/Stomatitis	29	33	18	8
Hepatic	10	11	14	2
Jaundice	3	8	7	0
Infections	66	73	60	43
UTI	7	2	7	2
pneumonia	9	7	9	0
sepsis	34	36	31	18
fungal infections	15	13	9	6
Renal Failure	8	6	0	2
Fever	78	71	24	18
Alopecia	37	40	22	16
Pulmonary	43	43	24	14
Cough	13	9	9	2
Dyspnea	18	20	6	0
CNS	30	30	34	35
Seizures	4	4	2	8
Headache	10	9	13	8
Eye	7	6	2	4
Conjunctivitis	5	1	0	0

Allergic Reaction: Hypotension, urticaria, dyspnea and rashes have been reported occasionally.

Cutaneous: Phlebitis has been reported infrequently at the site of infusion. There have been rare reports of tissue necrosis following extravasation.

Hematologic: Myelosuppression is rapid in onset and is consistent with the requirement to produce significant marrow hypoplasia in order to achieve a response. The incidences of infection and bleeding seen in the U.S. trial are consistent with those reported for other standard induction regimens.

Gastrointestinal: Nausea and vomiting occurred acutely in most patients, but were generally mild to moderate and could be controlled through the use of antiemetics. Stomatitis/mucositis occurs within one week of therapy.

Cardiovascular: Congestive heart failure, tachycardia, EKG changes including arrhythmias, chest pain and asymptomatic decreases in left ventricular ejection fraction have occurred (see WARNINGS).

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-297

DEC 23 1987

Lederle Laboratories
A Division of American Cyanamid Company
Pearl River, New York 10965

Attention: Dennis J. Foley, Ph.D.
Director
Regulatory Liaison

Dear Dr. Foley:

Reference is made to your new drug application dated May 18, 1984 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for NOVANTRONE (Mitoxantrone Hydrochloride Concentrate for Injection).

We also acknowledge receipt of your additional communications dated March 12 and 19, May 15, September 21 and 30, October 22, December 10, 22 and 23, 1987.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as initial therapy for acute nonlymphocytic leukemia (ANLL) in adults as recommended in the submitted draft labeling (package insert) as revised in the enclosure. In addition, the vial label and cartons must be revised as follows:

1. The vial and carton labels must be changed from NOVANTRONE Mitoxantrone Hydrochloride for Injection to NOVANTRONE (Mitoxantrone Hydrochloride Concentrate for Injection).

2. "AFTER DILUTION" must be emphasized (i.e., underline, block in yellow, enlarge or use different print) on the vial label and carton.

3. These revisions must be made immediately. However, your vial cartons for 20 mg (28,700), 25 mg (3,000) and 30 mg (3,000) of NOVANTRONE may be shipped with the provision that a prominent notice accompany each box of vials. This notice should, in bold print, clearly state that NOVANTRONE solution is a concentrate and must be diluted, and that revised labeling for the vial cartons will be implemented for further distribution of the drug.

Accordingly, the application, with the labeling revisions described above, is approved effective as of the date of this letter. Furthermore, it was agreed to on December 14, 1987 during a meeting with representatives of your staff, specifically, Drs. Kenneth Cartwright and Steven Saletan, and Dr. Gregory Burke and Ms. Aleta Sindelar of this Division, that your firm will continue to follow the patients entered in the controlled clinical trials in ANLL and to submit yearly updates of the survival data as well as data regarding possible chronic toxicities.

Although the submitted data suggest activity for NOVANTRONE in relapsed ANLL, there are no adequate and well-controlled studies contained in the submission that demonstrate its safety and effectiveness for relapsed or refractory ANLL. Due to the heterogeneity of these patient populations, well-controlled studies are necessary to demonstrate effectiveness for these indications.

Moreover, neither do the mature data submitted for use of NOVANTRONE for the treatment of breast cancer provide adequate evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in its proposed labeling as required under 21 CFR 314.125(b)(5). Specifically, Study 4-52 (NOVANTRONE versus ADRIAMYCIN) does not provide evidence that treatment of patients with advanced breast cancer with NOVANTRONE will favorably affect their quality of life or survival. The low response rate (15%) does not imply efficacy in view of the sometimes severe toxicity. The design and outcome of Study 3-48 [CYTOXAN + NOVANTRONE + FLUOROURACIL (CNF) versus CYTOXAN + ADRIAMYCIN + FLUOROURACIL (CAF)] does not permit a conclusion that NOVANTRONE when used in combination with CYTOXAN and FLUOROURACIL is effective. The comparable survival to CAF alone does not provide evidence that NOVANTRONE is independently effective in this combination because the role of the substituted drug in enhancement of survival in this combination is not established. The inferior response rate of CNF taken with the lower bound of the 95% confidence limit of the difference in response rate likewise does not provide assurance that NOVANTRONE contributes to this effect in this combination. Therefore, we consider the indication not approvable for the use of NOVANTRONE as a second line treatment of breast cancer or in combination therapy for front line therapy.

The enclosed revisions in the draft package insert are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested and previously agreed upon, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit twelve copies of the revised FPL when it is available. This submission should be designated for administrative purposes an "FPL Supplement" to the approved NDA 19-297. Approval of the supplement by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of this drug product become available prior to our receipt of the FPL, further revision of that labeling may be required. Further recommendations for revisions in the labeling may be requested at the completion of the review by the Division of Biometrics of the carcinogenicity studies submitted March 12 and 19, 1987.

You may propose, at a later date, to include a section in the package insert claiming an appropriate storage time for the diluted solutions upon the submission of supportive chemical and microbiological data.

Please submit one market package of the drug when it is available.

In addition, please submit, in duplicate, the advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Oncology and Radiopharmaceutical Drug Products, and the second copy to the Division of Drug Advertising and Labeling, HFN-240, Room 10B-04, 5600 Fishers Lane, Rockville, Maryland 20857. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drug Evaluation and Research

cc.
Original NDA 19-297
HFN-150/Div. File
HFN-100/RTemple
HFN-80
HFN-83
HFN-150/GBurke
HFN-730
HFN-232
HFN-150/AMSindelar/12-11 & 23-87
R/D Init by: G.Burke/12-14 & 23-87
J.R.Johnson/12-14-87/G.Burke for J.J.12-23-87
E.Tolgyesi/12-15-87
R.H.Wood/12-15 & 23-87
D.Richman/12-14-87
K.Y.Lo/elected not to sign
J.P.Skelly/elected not to sign
R.Stein/12-15-87
S.Dubey/12-15-87
R.G.Scully/12-15-87
R.Jerussi/12-16-87
J.F.Palmer/12-16-87
F/T:ke:12-23-87
Wang #2292E

APPROVED NDA